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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,674	11/13/2003	Ken Y. Lin	STAN-276	9855

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EXAMINER	
VENCI, DAVID J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 05/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/713,674	LIN ET AL.	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *January 13, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 15-19* is/are rejected.

7)☒ Claim(s) *16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 13, 2006, is entered.

Currently, claims 1-9 and 15-19 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claim 16 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 2. When two claims in an application are duplicates or are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112 – first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Independent claim 1 recites, *inter alia*, a method of detecting asymmetric dimethylarginine (ADMA) in a sample comprising ADMA and at least one of symmetric dimethylarginine (SDMA) and arginine. In step (a), an α-dicarbonyl compound is used to chemically modify SDMA and arginine. Thereafter, in step (b), ADMA is detected.

According to paragraph [0048] of Applicants' specification, a sample[1] is subject to SPE extraction, derivatization with *o*-phthaldialdehyde in the presence of methanol, borate and 3-mercaptopropionic acid (see para. [0048]). According to paragraphs [0034] and [0098] of Applicants' specification, an α-dicarbonyl compound (*e.g.*, phenylglyoxal dissolved in water, pH 9.0) is added to a sample, and a reaction is allowed to proceed anywhere from 15 seconds to 2 hours in the dark at room temperature. Applicants' specification contemplates one "modified SDMA" phenylglyoxal derivative (see Fig. 4) and one "modified arginine" phenylglyoxal derivative (see Fig. 2).

[1] The term "biological sample" encompasses a clinical sample, and also includes cells in culture, cell supernatants, cell lysates, serum, plasma, cerebrospinal fluid, urine, saliva, biological fluid, and tissue samples. See specification, paragraph [0016].

Applicants' specification does not describe a two-step method comprising the steps of: a) contacting a sample with an α-dicarbonyl compound, followed by b) detecting ADMA in the sample. Applicants' specification does not describe the exact experimental conditions for performing said two-step method comprising the steps of: a) modifying SDMA and arginine, followed by b) detecting ADMA in the sample. Applicants' specification does not describe the exact reaction conditions for reacting a sample with an α-dicarbonyl compound, resulting in detectable ADMA. Applicants' specification does not describe a detecting means capable of detecting ADMA in the product of a reaction between a sample with an α-dicarbonyl compound. Other than phenylglyoxal derivatives (see Figs. 2 and 4), Applicants' specification does not contemplate any other "modified SDMA" derivatives or "modified arginine" derivatives.

According to the decision in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), the factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the breadth of independent claim 1 is extremely broad. Claim 1 generically encompasses a method of detecting ADMA in any "sample", using any "α-dicarbonyl compound" and any "detecting" means.

Claim 1 does not specify whether/what sample clean-up steps may be required. Claim 1 does not specify any experimental parameters for carrying out the derivatization reaction.

The state of the prior art appears to recognize a high degree of unpredictability in the field of arginine chemical derivitization. For example, Baburaj *et al.*, 1199 BIOCHIM. BIOPHYS. ACTA 253 (1994), discovered two α-dicarbonyl compounds (see Title, "HOCGO" and "DMACGO") that produced unexpected, unpredictable results when used to derivatize samples. Specifically, Baburaj *et al.* discovered that HOCGO and DMACGO are: (1) capable of reaction with cysteine and lysine residues (in addition to arginine); (2) extremely sensitive to variations in solvent pH and polarity; (3) capable of reacting with samples that don't possess arginine; and (4) react with samples non-covalently (see p. 262, right column, Section 4.2). With respect to HOCGO and DMACGO, the findings of Baburaj *et al.* suggest that the ability of α-dicarbonyl compounds to distinguish between ADMA-containing samples versus non-ADMA containing samples may be somewhat limited using fluorescence-based detection.

According to Schwarzenbolz *et al.*, 205 Z. LEBENSM. UNTERS FORSCH. A 121 (1997), under certain reaction conditions, the α-dicarbonyl compound, glyoxal, produces two arginine derivatives (see Fig. 3). Similarly, Sopio & Lederer, 201 Z. LEBENSM. UNTERS FORSCH. A 381 (1995), teaches that, under certain experimental conditions, the α-dicarbonyl compound, deoxyosones, results in two tautomeric products (see Fig. 6). Based on Applicants' limited disclosure, whether these and other derivatives are contemplated, and whether these derivatives are distinguishable from ADMA is not clear.

Applicants' specification provides inadequate direction for carrying out the arginine derivatization reaction on "a sample." Paragraphs [0034] and [0098] of Applicants' specification provides the extent of direction, disclosing that an α-dicarbonyl compound (*e.g.*, phenylglyoxal dissolved in water, pH 9.0) is added to a sample, and a reaction is allowed to proceed anywhere from 15 seconds to 2 hours in the dark at room temperature. Examiner posits that the level of direction provided in paragraphs [0034] and [0098] of Applicants' specification is insufficient to enable persons of ordinary skill to perform a two-step method of

detecting ADMA comprising the steps of: a) contacting a sample with an α-dicarbonyl compound, followed by b) detecting ADMA in the sample. The working examples located on pp. 22-25 of Applicants' specification are inadequate for similar reasons.

Given the aforementioned deficiencies in Applicants' disclosure, Examiner posits that the quantity of experimentation needed to perform the claimed two-step method of detecting ADMA is undue.

Claim Rejections - 35 USC § 112 – second paragraph

Claims 1-9 and 15-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1:

The phrase "said sample is suspected of containing ADMA and at least one of SDMA and arginine" is indefinite. The phrase appears inconsistent with the preamble phrase "a sample comprising ADMA, symmetric dimethylarginine (SDMA), and arginine".

The object type mismatch "contacting resulting in modification" is indefinite. Whether the object(s) and/or steps required for performing "contacting" are coextensive with the object(s) and/or steps required for performing "modification" or "modifying" is not clear.

In claim 1, the recitation of the infinitive "to produce" is indefinite. Whether the act or process of producing is completed or performed, or merely intended, is not clear. The identity of object(s) and/or step(s), if any, required for performing producing is not clear.

In claim 1, the passive voice recitation "said modified SDMA and said modified arginine are distinguishable" is indefinite. The identity of object(s) and/or step(s), if any, required for performing distinguishing is not clear.

Response to Arguments

In prior Office action, claims 1-8 and 15-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Balint & Cooke (WO 98/49199) in view of Duerksen & Wilkinson, 160 ANAL. BIOCHEM. 444 (1987). In addition, claim 9 was rejected under 35 U.S.C. 103(a) as being unpatentable over Balint & Cooke (WO 98/49199) and Duerksen & Wilkinson, 160 ANAL. BIOCHEM. 444 (1987), as applied to claim 1, and further in view of Fishman et al. (US 5,318,680).

In response, Applicants argue that Duerksen & Wilkinson is non-analogous art. Accordingly, Applicants argue that: (1) there is no motivation to combine the teachings of Balint & Cooke with Duerksen & Wilkinson; (2) neither Balint & Cooke nor Duerksen & Wilkinson provide any reasonable expectation of success in combining their teachings; and (3) the combined teachings of Balint & Cooke and Duerksen & Wilkinson do not teach all of the claimed limitations.

Applicants' arguments are fully persuasive and sufficient to overcome these rejections. Accordingly, these rejections are withdrawn.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci
Examiner
Art Unit 1641

djv

LONG V. LE
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07/28/06